

## Case Report

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**Coagulation Disorder following Red Clover (*Trifolium Pratense*) Misuse: a Case Report**Sahar Karimpour-Reihan<sup>1\*</sup>, Elnaz Firuzei<sup>1</sup>, Malihe Khosravi<sup>1</sup>, Mahsa Abbaszade<sup>1</sup>

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**Abstract**

**Introduction:** An increasing variety of alternative health care products and supplements known as over-the-counter (OTC) or non-prescription herbal medicines are taken by patients for different reasons. Unfortunately, these self-prescribed remedies have many food and drug interactions and unknown adverse effects and can lead to some important consequences.

**Case presentation:** Here a case of bleeding disorder in a 28-year-old woman taking red clover is reported. She had no history of warfarin use, but warfarin was detected in her blood serum analysis.

**Conclusion:** This agent is a source of natural coumarin and can cause an increase of international normalized ratio (INR) and bleeding. It is important that prescribers be alert to the possible disadvantage of herbal remedies and also probable herb-drug and herb-food interactions.

**Key words:** Blood coagulation disorders; Hemorrhage; Herbal medicine; *Trifolium*; Warfarin

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**INTRODUCTION**

Over-the-counter (OTC) herbal agents are classified as dietary supplements and are not rigorously regulated by the US Food and Drug Administration (FDA). They are wrongly thought to have no complications, so herbal therapies are increasingly being used all around the world (1). Red clover (*Trifolium pratense*) is one of such herbs that has been used for various disorders such as skin ulcers, menopause syndrome, cough, sore throat, fever, pneumonia, meningitis, diarrhea, and hair loss (2-4). Red clover is a legume whose flower top contains more than 100 chemical substances including tannins, isoflavone phytoestrogen, flavonoids, essential oil, polysaccharides, saponins, phaseolic acid, and salicylic acid (2, 3). Red clover is also a source of natural coumarin and would be expected to enhance the effects of anticoagulants and antiplatelet agents (2, 5). Clover is used in the form of herbal tea in Iran. There is a mixture of red clover and alfalfa in Iranian traditional medicine which is sold, presumably, as a platelet count enhancer. Although the product information warns of the theoretical bleeding risks with red clover, there are limited clinical case reports of bleeding attributed to it. Here, we report a case with the clinical presentation of warfarin toxicity without warfarin ingestion.

**CASE PRESENTATION**

A 28-year-old woman was admitted to the

emergency department (ED) complaining of gross hematuria. She arbitrarily used a herbal supplement that contained red clover and alfalfa. The patient had been drinking this herbal tea a maximum of 5-6 cups every day for two consecutive weeks. After two weeks, few episodes of epistaxis occurred, and ecchymotic lesions developed on her limbs.

In the past medical history, she was diagnosed as a case of systemic lupus erythematosus (SLE) about five months back and had a history of idiopathic thrombocytopenic purpura (ITP) and low platelet count from that time. She was under treatment with prednisolone 1 mg/kg daily. There was no drug history of intake of anticoagulants. She had several episodes of bleeding and epistaxis that had been treated with fresh frozen plasma (FFP) and Vitamin K.

On physical examination, the positive findings included diffuse ecchymosis in her limbs and mild bleeding from her lips. At the time of admission to ED, she had a prothrombin time (PT) of more than 37 seconds, activated partial thromboplastin time (aPTT) more than 70 seconds, and international normalized ratio (INR) greater than seven. Other laboratory tests conducted at our hospital displayed the following results: white blood cell count  $9.80 \times 10^9/\mu\text{l}$ , hemoglobin 11.8g/dL, and platelet count  $406 \times 10^9/\mu\text{l}$ . The results of the liver and renal function tests were within the normal

range. The level of coagulation factors were as follows: factor II 18% (normal range: 70–120); factor V 94% (normal range: 60–130); factor VII <1% (normal range: 55–190); and factor X 7% (normal range: 70–120). The fibrinogen level was 303 mg/dl (200–400). A mixing test was performed that was normal. Therefore, the main clinical suspicion in this patient was poisoning by a vitamin K antagonist. This suggestion was confirmed by the detection of warfarin in the patient's blood sample; however, our patient did not have any history of warfarin or super-warfarin consumption. The patient was treated empirically with 20 mg of intravenous vitamin K and four units of FFP within 10 days of hospitalization. In that time, the bleeding stopped, and laboratory parameters returned to normal range (PT = 11.5 seconds and INR = 1). She was discharged and was advised not to use herbal supplements without a physician prescription.

#### DISCUSSION

Identifying the cause in patients with coagulation disorders could be difficult. There may not always be a history of herbal exposure, and the initial clinical presentation is not always clear, which can affect the physician's ability to make the diagnosis. Other diagnostic considerations in a patient presenting with coagulopathy of unknown origin include warfarin or super-warfarin exposure, disseminated intravascular coagulation (DIC), vitamin K malabsorption, and pathologic inhibitors of coagulation (6). Lupus anticoagulant factor as a cause of bleeding and increased PTT in this patient with a history of SLE was ruled out by the normal mixed test results and inactive SLE. Liver dysfunction as a major cause of increased PT and

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INR and decreased vitamin K dependent coagulation factors was ruled out in our patient by the normal liver enzyme levels, serum albumin concentration, and especially, normal serum factor V level which is another coagulation factor that is synthesized by the liver. High consumption of coagulation factors seen in DIC was ruled out in our patient by the high concentration of serum factor VIII (7).

Overall, when a patient presents with hemorrhagic coagulopathy and prolonged PT and aPTT values of unknown cause, testing for poisoning with warfarin-like compounds should be considered. On the other hand, it is important that prescribers be alert to the possible disadvantage of herbal remedies and also probable herb-drug and herb-food interactions.

#### CONCLUSIONS

This case report showed the probability of toxicity of warfarin-like compounds causing significant coagulopathy following Red Clover misuse.

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#### AUTHORS' CONTRIBUTION

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

#### CONFLICT OF INTEREST

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